Chemistry & Biology

In This Issue

Small Molecule Blocks Ligand-dependent TNF Receptor I Endocytosis

PAGE 1105

While biologic drugs such as anti-TNFα antibodies and soluble TNFα receptors have made significant impact on human health, there is an increasing demand for small molecule inhibitors that control TNFα function. The study by Gururaja et al. highlights the discovery of a class of small molecule TNFα antagonists that inhibit most of the TNFα functions via blockade of ligand-dependent receptor (TNFαRI) endocytosis, resulting in disruption of TNFαRI/TRADD/RIP1 interactions. These triazoloquinoxaline (TQ)-based compounds modulate both TNFα-induced survival and apoptotic pathways; such dual activity makes them unique, since compounds targeting only a subset of TNFα signaling pathways (e.g., IKK and proteasome inhibitors) increase TNFα-induced cytotoxicity.

Targeting Quorum Sensing as New Antibacterial Strategy

PAGE 1119

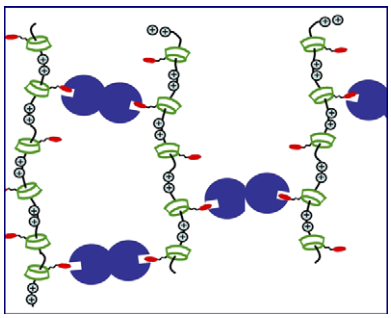
Bacteria have evolved an elaborate small molecule-based communication system called quorum sensing (QS). QS plays an important role in mediating bacterial virulence, and it constitutes a newly emerging target for development of antibacterial agents. Park and colleagues report an immunopharmacotherapeutic approach for the attenuation of (QS) in the Gram-positive human pathogen *Staphylococcus aureus.* An anti-autoinducer monoclonal antibody was elicited against a rationally designed hapten and was shown to efficiently inhibit QS in vitro. Importantly, the anti-autoinducer antibody suppressed *S. aureus* pathogenicity in an abscess formation mouse model and provided mice with a complete protection against a lethal *S. aureus* challenge. These findings build a strong foundation for further investigation of using immunopharmacotherapy for the treatment of bacterial infections in which the expression of virulence factors is under QS control.

Investigating Complexity of Gold(III)-dithiocarbamato Complexes

PAGE 1128

Gold(III)-dithiocarbamato complexes are promising chemotherapeutics able to exert outstanding cytotoxic activity toward tumor cell lines. Furthermore, they induce a strong downregulation of Bcl-2 and upregulation of Bax proteins and inhibition of proteasome activity, but only weak perturbations of cell cycle. In the paper by Saggioro et al. the complexes' mechanism of action was analyzed by means of cellular, biochemical, and molecular approaches. The authors show that gold(III)-dithiocarbamato complexes induce cancer cell death through both apoptotic and nonapoptotic mechanisms. A working model, suggesting that deregulation of the thioredoxin reductase/thioredoxin redox system is a major mechanism involved in the anticancer activity of the investigated compounds, was proposed and discussed.

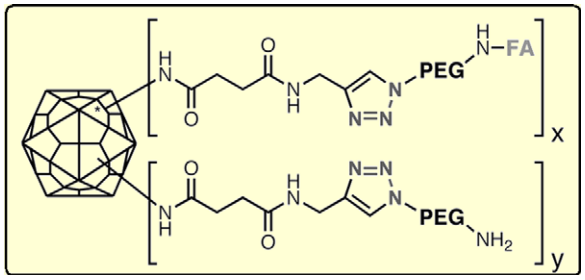
Multivalent Interactions with "Beads on a String"



PAGE 1140

The role of flexibility and adaptability in multivalent binding events is an intriguing question of molecular recognition with special relevance to glycobiology. Belitsky et al. have investigated the interactions between self-assembled multivalent supramolecular complexes known as pseudopolyrotaxanes and a bivalent lectin, galectin-1. The pseudopolyrotaxanes are comprised of lactoside-displaying cyclodextrin "beads" threaded onto polyviologen "strings," which provide a flexible and adaptable presentation of lactoside ligands. These self-assembled complexes are useful tools for the study of multivalent interactions—and more broadly—suggest that the conceptually related, but often disparate, fields of supramolecular chemistry and biochemistry have much to offer each other.

Targeting Viral Nanoparticle to Tumor Cells



PAGE 1152

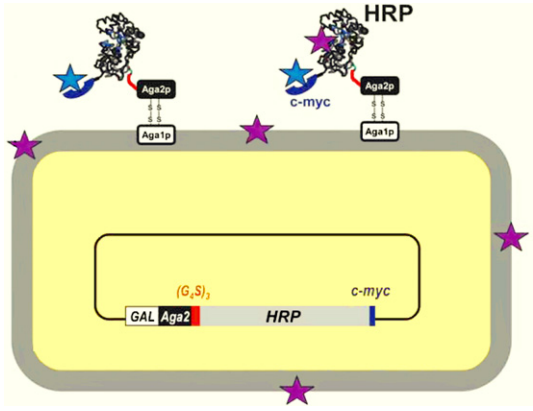
The ability to specifically target therapeutics and imaging modalities to tumors is an important goal in biomedicine. Viral nanoparticles (VNPs) such as cowpea mosaic virus (CPMV) provide tremendous imaging resolution of normal and tumor vasculature; however, the particles have significant affinity for cell-surface proteins. To mask any natural in vivo interactions of CPMV, "click" chemistry was used to attach folic acid tumor ligands, while redirecting the natural specificity of the particles by coating the remaining surface of the particles with polyethylene glycol. The resulting particles demonstrate that effective retargeting of VNPs may be mediated by small molecule ligands.

Mechanism-of-Action (MOA) Determination of GMP Synthase Inhibitors

PAGE 1163

Compound mechanism-of-action (MOA) study and target validation are crucial aspects of drug discovery. Using a chemogenomics approach, the *Candida albicans* fitness test, Rodriguez-Suarez and colleagues conducted MOA analyses for several compounds affecting purine metabolism, and identified a novel antifungal compound (ECC1385) as a potent inhibitor of GMP synthase, which is encoded by the *GUA1* gene. The authors further demonstrated, in both *Candida albicans* and *Aspergillus fumigatus*, that genetic inactivation of the *GUA1* gene rendered the pathogens completely avirulent in murine infection models, thus validating *GUA1* as an unexpected antifungal target.

Selecting Horseradish Peroxidise Variants via Yeast Surface Display



PAGE 1176

The first application of yeast surface display to in vitro selection of altered enzymatic activity was presented by Lipovšek et al. The use of a eukaryotic organism to display the enzyme under selection makes possible in vitro evolution of a number of enzymes that cannot be expressed in a soluble and active form in bacteria, such as highly disulfide–crosslinked enzymes. In this study, the authors selected variants of horseradish peroxidase with up to an 8-fold altered enantioselectivity, including its reversal, from an active-site-directed library. In contrast, a library of similar size constructed using error-prone PCR yielded no HRP variants with a significantly improved enantioselectivity.

Allosteric Inhibition of the RUNX1 and CBFβ Interaction

PAGE 1186

Numerous inhibitors of enzymatic activity have been developed, but the development of inhibitors of protein-protein interactions has only recently come to the forefront as a viable approach. Allosteric inhibition of such protein-protein interactions presents a number of advantages, including not having to compete for binding with the partner protein; however, to date there are very few examples of such inhibitors. Gorczynski et al. have developed novel allosteric small molecule inhibitors of the binding of RUNX1 to CBFβ, two proteins whose translocations play a critical role in the development of acute myeloid leukemia and acute lymphocytic leukemia.

